Review article

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Opioid-induced hyperalgesia as a problem in pain management. Mechanisms of onset, diagnosis and treatment

Abstract

Opioids have been used for centuries to control pain. One of the problems with their use is the development of tolerance in some patients. This problem is usually solved by an increase in the dose. However, this does not solve all the difficulties encountered. In some patients, the opioid doses needs rise very quickly. It seems that this phenomenon depends on changes in the opioid receptors and on the organization of the functions of the central nervous system. This phenomenon is known as opioid-induced hyperalgesia. Changes may include the facilitation of pain conveyance which may more or less counteract the analgesic effect of the same drug. Until now, several putative mechanisms have been identified. Here we shall explore the changes of opioid receptors and changes in the glutaminergic system. In addition, the spinal cord and probably also the liver are producing a specific peptide, Dynorphin A, which has an excitatory effect. The organization and function of the On-Off cells in the brain are also changed. In this article, we discuss strategies for the treatment of opioid-induced hyperalgesia. These strategies have the potential to improve the quality of opioid analgesia.

Key words: pain, hyperalgesia, opioid-induced hyperalgesia, opioids, naloxone

Introduction

Opioids have been used for pain control for centuries. The analgesic effects of these drugs, however, is compromised by several negative (read neuroexcitatory) phenomena. These phenomena not infrequently complicate treatment and sometimes explain poor pain control and reluctance in opioids being prescribed. We are talking here about tolerance and addiction to opioids. Opioid-naive patients usually experience considerable decrease of pain sensations. This effect correlates strongly with the presence of opioid receptors and the plasma levels of the drugs and their metabolites. The analgesic effect also has a positive correlation to the dose of the drug administered. Immediately after the first administration of the drug, the central nervous system starts to adapt to it. This adaptation may imply that the patient is tolerant to opioids and higher doses of the drug will be needed to achieve the same pharmacological effects. Until now it was thought that tolerance to opioids was mainly related to the changes in opioid receptors. New drugs were invented with a stronger and more specific effect on opioid receptors. However, this approach certainly did not solve problems of tolerance. On the con-

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trary, the more potent opioid drugs seemed to induce tolerance more quickly and, as it now appears, are prone to inducing more pain. This phenomenon was called paradoxical pain in the past but only recently was this changed to opioid-induced hyperalgesia. This phenomenon can best be characterized by the lowering of the pain threshold. Hyperalgesia as such is encountered in many clinical situations. Here we shall focus on hyperalgesia induced by opioids. This phenomenon was suspected for a long time, as it was known that patients addicted to opioids present with a lower pain threshold and higher sensitivity to pain [1]. One of the strongest and most promising opioids, remifentanyl, appeared to induce potent analgesia during its use but after its discontinuation might induce even more pain which results in higher consumption of other opioids. [2, 3]. Thus it seems plausible that in spite of antinociceptive effects, opioids may also have a pro-nociceptive effect. This effect may form a background for the development of addiction, as each trial of the discontinuation of opioids results in more pain and the immediate recommencement of opioids administration.

In this article we shall focus on explanations of the mechanism of hyperalgesia and the significance of this phenomenon in the clinic. We shall also clarify how to recognize this phenomenon in clinical practice and also indicate how to prevent it.

Data from animal models

Analgesics were, for many years, tested using the tail-flick test in rats. This test is sensitive in detecting the potency of the drug but is totally insensitive to the detection of a lowered pain threshold. This is also the reason why many new potent opioids were developed without any idea about the pain threshold lowering capacity. Another procedure utilizing the slow-rising stimulation curve, such as the paw withdrawal test [4], is able to detect a lowering of the pain threshold, however. Using this test, it was shown that the 7-day-long administration of morphine to rats causes a progressive lowering of the pain threshold. Similar results were obtained after the subcutaneous administration of fentanyl [5, 6]. In these studies, it was shown that the lowering of the pain threshold persisted for at least five days after discontinuation of the drug. These data were also replicated for diacetylmorphine [7]. Opioid analgesics, therefore, produce not only anti-nociception but also pro-nociception which can be measured as a lowering of the pain threshold.

Clinical data

The pro-nociceptive effects of opioids had been suspected for a long time but it was difficult to show unequivocally [1]. The studies with remifentanyl were decisive, where lowering of the pain threshold was shown [8]. However, Cortez et al [9], in very similar circumstances, found something completely opposite. The studies with addicted subjects were very interesting [10]. In these patients, the lowered pain threshold following the prolonged use of opioids appears to have been detected even many years after the cure of addiction. Everybody who occasionally treats pain in terminally ill, former addicts, will know that the pain treatment in those subjects is much more difficult. In cancer patients, there is probably an additional hyperalgesia due to the tumour itself [11]. Lowering of the pain threshold was until now always interpreted as tumour progression and the pro-nociceptive effects by opioids were not taken into account.

Mechanisms of opioid-induced hyperalgesia

Until now, mechanisms contributing to the development of hyperalgesia were divided into two groups: one group contains those mechanisms responsible for desensitization (development of pharmacological tolerance at the level of the opioid receptors); the second is characterized by sensitization to pro-nociceptive effects (this can be measured as a lowering of the pain threshold). This latter group plays a role at the level of organization of the whole central nervous system, not only its opioids component. It is unknown how these mechanisms can be clinically differentiated from each other and it is probable that both types of mechanism may operate in the same subject and at the same time.

Desensitization of opioid receptors

One of the most exciting hypotheses was proposed and corroborated by Crain and Shen [12, 13]. According to these authors, peptide parts of opioid receptors are coupled to Gi/Go proteins [12]. These protein complexes are of an inhibitory nature. Interaction of this complex with an opioid will induce inhibitory effects such as the inhibition of pain conveyance, depression of the respiratory centre, inhibition of saliva production, constipation, and also somnolence. Even after the first dose of opioids (in

opioid-naive patients) the synthesis of GM1 ganglioside increases in the neural tissues. This protein causes uncoupling of the receptor peptides and coupling with another, Gs protein. These complexes are of an excitatory nature and after their stimulation with opioid agonist they will cause hyperalgesia, an increase in the respiratory rate, confusion and delirium. For unknown reasons, increase in salivary production and diarrhoea are not observed.

A change in at least some of the receptors from inhibitory to excitatory mode can not only explain phenomena such as opioid tolerance but also tolerance to respiratory depression due to opioids. Patients who receive opioids for a long time, respiratory depression after an increase of the opioids dose is only rarely seen.

Many doctors think that an increase of the opioid dose will not only improve the analgesic effect but also induce somnolence or even sedation (ethical issues concerning this are out of the scope of this paper). In fact, in many patients an increase of the opioids dose, instead of causing somnolence (inhibitory effect), will induce confusion and delirium (excitatory effect). As confusion is usually the reason for increasing the dose (is the patient not confused because of pain?), the results are easily predicted.

Excitatory effects are related to the synthesis of GM1 protein. Some patients probably have multiple gene copies for this protein. In these patients, one can see rapid development of tolerance to opioids. Other patients, with low or "normal" synthesis of GM1, may use opioids for many years without developing tolerance.

Complexes in excitatory mode are 1000 times more sensitive to naloxone than the inhibitory complexes. This prompted some researchers to use ultra low doses of naloxone to selectively inhibit the excitatory but not inhibitory complexes. Blocking the excitatory complexes with oseltamivir [14] has exactly the same effect and improves the effectiveness of analgesics but may also cause (transient) respiratory depression.

Few clinical trials have confirmed that ultra low doses of naloxone are able to improve opioids analgesia while higher doses block both inhibitory and excitatory receptors and decrease the analgesic effect of opioids.

It is possible that in humans with an increased capacity to synthesize GM1 protein the sensitivity to pain is also increased. It is also possible that in the pathogenesis of some pain syndromes, opioid-peptides synthesized in the liver are playing an important role. Their synthesis can be increased in such conditions as hepatitis, primary biliary cirrhosis, liver metastases and cholestasis. Pathologically increased synthesis of endogenous opioids in the liver, depending on the mix of opioids synthesized, may be responsible for spontaneous analgesia, hyperalgesia and hepatogenic itch. All three conditions can be reverted by naloxone. Antagonist to opioid peptides have been discovered in the central nervous system [15] and in that way these peptides may modulate the sensation of pain and itch.

Despite the fact that this hypothesis is well corroborated and the effects of ultra low doses of naloxone have been observed by many authors, this phenomenon is still controversial [16, 17]. One of the explanations of this is that different doses of naloxone were used in different protocols and the dose-interval in which naloxone is active is probably very narrow. We need more studies in order to solve these intriguing problems.

Sensitization of the Central Nervous System

Undoubtedly, the glutaminergic system plays an important role in sensitization of the central nervous system. Stimulation of the N-methyl-D-aspartate (NMDA) receptors generates pain facilitation which, to a large extent, escapes opioid control [18]. Stimulation of the NMDA receptors can result from the effect of opioids but it may also be independent of them. NMDA receptors can be stimulated by damage to the central nervous system (neuropathies) and chronic pain independent of such damage. Here, neuropathic pain and hyperalgesia suddenly have a common denominator and, probably, similar treatment methods.

Inactive NMDA receptors are blocked by bivalent magnesium ions. Hypomagnezemia may result in the opening of the NMDA channels and cause pain facilitation. In patients with hypomagnesaemia, hyposensitivity to opioids is frequently seen. Administration of magnesium sulphate can restore sensitivity and result in the increased toxicity of opioids. It should be added that longitudinal administration of opioids by itself can lead to displacement of magnesium ions and to their deficiency [19].

Ketamine is a specific inhibitor of the NMDA receptors and is used to decrease development of tolerance to opioids when the patient needs very high doses of opioids [20], and in some types of neuropathic pain [21]. It was suggested that brief (5–7 days) treatment with high doses of ketamine (the so called burst-ketamine) may lead to interruption and reset of hyperalgesia. This kind of treatment, pro-

viding it is well tolerated, may lead to pain reduction even for several weeks [22]. At the moment, we do not have any evidence for this from the controlled trials.

Dynorphine A

There is ample evidence that Dynorphine A of spinal origin is responsible for the phenomenon of opioid-induced hyperalgesia [23]. It appears that Dynorphine A increases sensitization of the spinal cord through the release of prostaglandins (PGE2), which stimulate the release of neurotransmitters (glutamate, substance P), and which are the normal responses to electrical stimuli from the periphery [24]. Dynorphine A belongs to the family of endogenous opioids. In painful conditions, under the influences of opioids, it may be produced in the spinal cord, as well as in the liver [25]. Dynorphine A is released in the spinal cord after longitudinal administration of opioids and in chronic pain. Increased concentrations of pro-dynorphine, the precursor of Dynorphine A, can also modify function of the NMDA receptors [24]. The increased activity of stimulating neuropeptides is not a specific response to opioid administration. Increased activity of Vasoactive Intestinal Peptide (VIP), Dynorphine (DYN), Cholcystokinine (CCK) and Neuropeptide Y (NPY) is seen after damage to the nerves. Again, neuropathic pain and hyperalgesia are not very different from each other. Clinically, those two conditions can easily be confused.

Descending control of pain impulses

The Rostral Ventromedial Medulla (RVM) contains the so-called "On-Off" neurons which are sensitive to opioids [26]. Stimulation of these neurons can lead to facilitation of pain conveyance by the ascending pain pathways [27]. Pain facilitation in the spinal cord can also occur as a result of synthesis of excitatory neuropeptides.

Not much is known about the integration of these factors. Such studies are difficult and cumbersome. Inhibition of all known elements at the same time results in the reversal of hyperalgesia. However, development of tolerance to opioids could be inhibited by the antibodies against Dynorphine A but not after inhibition of the NMDA receptors [18]. This suggests that the activity of Dynorphine A is related to the development of tolerance and this mechanism has an overlap with the mechanisms that lead to a lowering of the pain threshold.

Clinical picture of hyperalgesia

It had already been noticed a long time ago that prolonged use of analgesic opioids may result in a decrease in their effectiveness. Doctors usually coped with this phenomenon by increasing the opioid dose, as long as the drugs did not cause cumbersome adverse effects. It was thought that in cancer an increase in nociception due to progressive disease was the reason for the increased needs of opioids. The fact that opioids may lower the pain threshold was nearly never considered. The need to increase the dose of opioids is well documented and from time to time it may be a difficult problem, especially in longer prognoses.

Patients who develop opioid-induced hyperalgesia may present with the following signs and symptoms. An acute, breakthrough dose of opioid may be successful, while increasing the dose of slow release drugs or drugs administered in a syringe driver may be ineffective or help only for a short time. Usually, one or two days after the increase, there is a dilemma as to whether or not to increase the dose again. The second phenomenon is the generalization of the pain. The primary pain symptom (pain localization), not infrequently related to the known localization of the tumour, may be well controlled with opioids but the patient reports that the character of the pain changes as the pain symptoms are more generalized. Not infrequently, the skin is very sensitive to pinprick and touch (hyperalgesia and allodynia). If not specifically asked, the patient may confuse those symptoms. The same phenomenon is well documented after longitudinal administration of spinal morphine [28–30] and sufentanyl [31]. In this last case, because of the specific character of this drug, hyperalgesia occurs mainly on the lower extremities [31].

Lowering of the pain threshold may be assessed by the cold pressor test. A patient's hand is immersed in ice-cold water (0°C) and the time before withdrawal is measured. A shortening of the time before withdrawal may indicate a lowering of the pain threshold. This test is performed before and during treatment with opioids.

In the case of opioid tolerance (so-called pharmacological tolerance), an increase in the opioid dose leads to an increase of the analgesic effect. In the case of pure tolerance, the character of the pain does not change, providing there are no new anatomically explainable pain localizations (for example new bone metastases).

Management strategy

In the case of opioid-induced hyperalgesia, the best initial strategy is a lowering of the opioid dose. Sometimes, it is difficult to convince the patient to do so. Analysis of dose mistakes can be helpful. Omission of one dose or failure to remove the fentanyl patch after 72 hours may have, for a while, effects on pain which are different from expected. Taking a detailed history from the patient is of paramount importance. The pain may increase or decrease and the patient may show symptoms of abstinence. Usually, in the case of hyperalgesia, a gradual decrease of the dose by 25–30% may increase the analgesic effect.

Opioid-induced hyperalgesia and opioid tolerance should be differentiated from the intrinsic resistance of some types of pain to opioids. Although the pain mechanisms may overlap, some neuropathic pains may be resistant or only partially sensitive to opioids. In the case of such a pain, it is better to start co-analgesics. Drugs like anticonvulsants and antidepressants may be effective here. It is important, after achieving pain control, to switch these drugs and decrease the doses of opioid analgesics in order to avoid or limit the development of hyperalgesia.

In case one opioid is not effective, another may be tried. This procedure is known as opioid switch or rotation. It looks as if opioid-induced hyperalgesia may develop with one but not necessarily with other opioids. This phenomenon is known as partial tolerance. Unfortunately, after a switch to another opioid, analgesia may be improved but hyperalgesia will usually develop after some time. In one study concerning the effectivity of an opioid switch, seven switches were used [32]. However, a new way of switching has recently been described. This new method, called "semi-switch", includes a decrease in the dose of the first opioid and adding a new opioid [30].

Buprenorphine

It looks as if opioids may differ in their ability to provoke hyperalgesia. In a model of hyperalgesia induced in volunteers by an electrical current, it was shown that there are considerable differences between opioids in their ability to deal with hyperalgesia (antihyperalgesia effect). Fentanyl and its derivatives showed potent analgesic effect in this model, but only weak antihyperalgesic effect, while buprenorphine and ketamine-S showed weaker analgesic effect but a potent antihyperalgetic effect [33]. Clinical data to support this observation are still missing. However, it looks as if buprenorphine may be an interesting drug in the case of endogenous hyperopioidaemia, where the synthesis of endogenous opioids (in the liver) is increased. These phenomena are known to induce itch of cholestasis [34]. There are suggestions that a damaged liver (as a result of cholestasis, liver metastasis and others) is able to produce high amounts of endogenous opioids. These opioids, probably depending on their mix, may precipitate itch, hyperalgesia or hypoalgesia [35].

Buprenorphine, with its high affinity for the opioid receptor but only a weak stimulation (efficacy), may act like an antagonist, similar to naloxone in blocking access to the opioid receptors for endogenous opioids. This kind of effect helps to understand why buprenorphine may be effective in the treatment of hepatogenic itch [36]. It is possible that the antihyperalgesic effect of buprenorphine is an important element in its unusual "analgesic" properties. The recent introduction of a new formulation of buprenorphine in patches will certainly boost interest in these effects. We may soon expect new and interesting data from clinical trials. Until now, the feared ceiling effect of buprenorphine has not been shown in humans [37].

Ketamine

In the case of pains resistant to opioids, ketamine may offer an interesting additional effect [38]. Despite positive results in the treatment of cancer pain, systematic analysis could not (so far) establish equivocal conclusions [20]. Ketamine can be used orally together with morphine or other opioids [39]. Sometimes ketamine needs to be administered parenterally, usually in a subcutaneous syringe driver [40]. Recently published data on burst-ketamine protocols have been exceptionally interesting. Ketamine is used in relatively high doses for several days. After discontinuation of treatment, the analgesic effect persists for several weeks [22].

Magnesium sulphate

Another strategy to deal with the problem of hyperalgesia is the administration of magnesium sulphate, especially where magnesium deficiency can be present as in patients treated in the past with cis-platin. These patients may have damaged renal tubules and may not reabsorb magnesium from urine. In addition, a rapid growth of tumour mass may lead to increased magnesium losses. Another risk

factor is chronic diarrhoea or a short bowel syndrome due to, for example, an ileostomy. All these conditions may lead to hypomagnesaemia. Unfortunately, magnesium is poorly absorbed from the gastrointestinal tract and the preferred way for its administration is intravenous infusion [41]. Doses of several grams of magnesium sulphate per day are not infrequent. Administration in one intravenous shot is not advisable and may be dangerous. After parenteral administration and equilibration, magnesium can be administered orally in the form of magnesium hydroxide, usually in combination with calcium gluconate. Plasma magnesium concentrations are not representative for magnesium stores because most magnesium is found intracellularly and not in plasma. Excretion of magnesium ions from the cells may increase plasma levels while the cells themselves may be depleted of this ion. In contrast, low plasma magnesium invariably shows a magnesium shortage. More reliable is the magnesium retention test [42]. A patient receives a certain dose of magnesium sulphate intravenously and its excretion in the urine is measured. It is believed that magnesium retention correlates to magnesium deficiency. Even patients who eat well may develop magnesium deficiency in different pathological states as well as with stress. Magnesium in our diet has decreased by half in the last 100 years. Many drugs which were used frequently in the past, and which contained magnesium ions (laxatives and antacids), are not in use any more.

Ultra low doses of opioid antagonists

The hypothesis that ultra low doses of naloxone are able to improve quality of opioid analgesia and diminish at least some adverse effects of opioids is very interesting. The dose interval in which naloxone would be able to have this effect is probably very narrow and possibly different in different individuals. This is probably the reason why this method has not been investigated widely and why the existing clinical data are contradictory [16, 17]. From personal experience, we can say that naloxone can be useful in different clinical situations. We have tried using naloxone in more than 40 patients with, we must say, mixed results. Most of the patients used naloxone as the last resort treatment when their pain was unrelieved and the patient was receiving very high doses of opioids. It is important to state that all patients started with 3 mcg/kg/24 hours. The results, if any, were seen within several hours after beginning the infusion. In several patients, apart from better control of the pain, we observed (slight) respiratory depression. A decrease in the excitatory effect on the respiratory centre is one of the most interesting effects of naloxone, objectively confirming the hypothesis of "inverted" opioid receptors. It is now obvious that naloxone does not solve many problems but instead creates a new one. After several days of treatment, the patient experiences local irritation and inflammation at the infusion site in the case of subcutaneous administration. Naloxone cannot be administered orally as its oral bioavailability is not higher than 1–3%. In several cases treated by us in the Netherlands it was possible to administer a water solution of naltrexone which was prepared after dissolution of the tablet. We do not know the shelf life of such a solution and further research is hampered because of this. Several people treated with oral naltrexone (once daily 1–5 mcg/24 hours) benefited greatly from this treatment. One patient with a non-malignant pain has already been treated with naltrexone for 5 years. We still hope that this drug will be investigated formally as an adjuvant analgesic.

Clonidine

Clonidine is an alpha-2 agonist adrenergic drug, which has been used for a long time in the treatment of arterial hypertension. As well as its blood pressure lowering effects, clonidine is used in the treatment of symptoms of opioid abstinence [43]. As has already been stated, opioids may not only induce analgesia but also hyperalgesia. After sudden discontinuation of opioids, patients, among other abstinence symptoms, may experience the severe pain of hyperalgesia. This hyperalgesia may be sensitive to clonidine. Clonidine is frequently used spinally, together with morphine [44–47]. Clonidine can be used in subcutaneous infusions as an adjuvant treatment when the patient develops a rapid tolerance to opioids. We do not have much clinical experience with this drug. However, further studies are certainly worthwhile. It is important that candidates for this treatment have at least normal blood pressure and that this parameter is monitored during treatment.

Conclusions

Administration of opioids to relieve pain may also cause hyperalgesia. This second phenomenon is only seen in some patients but it may explain the development of tolerance, addiction to opioids and

pain insensitivity to opioids. There are several different strategies for dealing with hyperalgesia. One of the basic principles is obtaining normal body magnesium stores. This can be done by the intravenous infusion of magnesium sulphate. If magnesium sulphate infusion is ineffective, one can use ketamine or ultra low doses of opioid antagonists. The most effective strategy, however, is lowering the dose of opioids. Very promising is the use of partial agonists like buprenorphine in patches. Buprenorphine seems to be one of the few opioids which do not produce hyperalgesia. We certainly need more studies on this.

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